Selegiline HCl Tablets, USP, 5 mg
ANDA # 74-912
Reviewer: Hoainhon Nguyen
WP # 74912sd.d97

Stason Pharmaceuticals, Inc.
Irvine, CA
Submission Date:
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Review of a Study Amendment (for a Fasting Bioequivalence Study and a Non-Fasting Study) and Dissolution Data

I. Background: Responses to Deficiency Comments and Comments on Responses

The firm has submitted a study amendment in response to the deficiency comments by the Division of Bioequivalence in the letter to the firm dated September 29, 1997. The two bioequivalence studies and the first study amendment were reviewed by Larry Ouderkirk (February 28 and September 18, 1997). The summary of the deficiency comments and the firm's responses to the comments is given below.

Deficiency Comment #1:

(First Part) ***The Division of Bioequivalence finds that the quality control criteria, as described in SOP 2D-11.2, may not provide optimum assurance of adequate assay performance, especially considering that the criteria do not provide for duplicate QC samples at each control concentration. Also, while the current criteria provide for repeating certain samples in a section if the High or Extra-Low QC samples in that section differ by more than ±20% from the target concentration, the criteria do not consider the possibility that the second-lowest (Low) or second-highest (Medium) QC samples may also fail the ±20% limits. In those cases, the current policies on repeat samples would be clearly inadequate.***

Firm's Response #1 (First Part):

"According to it was not statistically justified to use duplicate QC samples to judge a run of unknowns, unless unknown samples were also run in duplicate." "SOP 2D-11.2 limits the controls that are outside ±15% of the target concentrations, except that the High

and Extra Low controls must be within ±20% (not 20.1%). Dilution controls also have a ±15% acceptance limit for over the curve samples, acceptance was judged based on diluted samples." and "if the Extra-Low and Low controls exceed the ±20% limit, then samples with concentrations below the Medium control must be repeated."

The assay was characterized by *"the relatively large range differences among selegiline (25 pg/ml to 3,000 pg/ml, 120 fold), N-desmethylselegiline (100 pg/ml to 28,000 pg/ml, 280 fold range), amphetamine (100 pg/ml to 4,000 pg/ml, 40 fold range) and methamphetamine (100 pg/ml to 15,000 pg/ml, 150 fold range) and the limited linearity range of the (in general, up to a 150 fold range)"*, and *"some samples require dilution for over the standard curve range and . Yet the same sample must be reassayed without dilution due to the sensitivity requirement for selegiline, while the volume of the sample must be delicately balanced to provide acceptable results. Thus, over the standard curve range, and four chemicals in ith the complications in SOP 2D-11.2 criteria for choosing repeats in the QA/QC inpection was dealt simultaneously."*

Division's Comment #1(Part One):

The firm's response above is adequate.

Deficiency Comment #1 (Part Two):

We suggest revising the quality control acceptance criteria to conform more closely with those in the guideline by Shah, et al. (Pharmaceutical Research, Vol.9, No.4, 1992). In particular, the criteria should be revised to require that duplicate Q.C. samples be assayed with each section (or run) of unknown samples. The requirement that two-thirds of the samples should assay within ±20% of the target concentration and that no two duplicate samples at the same concentration should be permitted to fail the accuracy criteria should also be specified in your SOP. In the event Q.C. samples fail to meet the pre-determined acceptance criteria, the revised SOP should also specify which of the unknown samples in the section/run should be re-assayed, and also should specify a policy for repeating re-assayed samples, should those runs also fail the QC criteria.

Firm's Response #1 (Part Two):

The firm agrees to revise the SOP pertaining to repeat testing for future studies in compliance with the FDA guidance. *"However, since the protocol for repeats as well as other facets of a study should be established* a priori, *and since the final results used the criteria as explained earlier, the DSU 95-A035B and C reports for this submission were based on the repeat SOP 2D-11.2 criteria. It would be very difficult to re-evaluate these results with new criteria established after running the studies."*

Division's Comment #1(Part Two):

The firm's response is adequate.

Deficiency Comment #2 (Part One: On Fasting Study):

2. *The Division has reviewed your revised quality control data for fasting study #1627 (#95-A035B) and for a food effects study #1666 (#95-A035C) and we have the following comments:*

   On the fasting Study #1627 (#95-A035B) -

   a) *The lists of repeat sample assays originally submitted 5/31/96 in Tables 2A, 2B, 2C and 2D, (for selegiline, desmethylselegiline, amphetamine, and methamphetamine, respectively), do not agree with the detailed repeat sample data supplied in the submission of 5/12/97 in Tables 3A, 3B, 3C, and 3D. For instance, in Table 3D for methamphetamine, many more repeat sample assays are now documented than were listed in Table 2D in the original report. We advise submission of revised Tables 2A, 2B, 2C, and 2D to completely and accurately report the reassayed sample data. Additionally, submit revised assay results tables giving the assayed values of the control samples and unknowns in terms of drug or metabolite concentrations (in ng/mL), rather than only as intensity ratios, as now reported to allow greater ease of cross-checking the*

data. The revised results tables should be organized by assay runs, rather than by subject number, to better correlate with the assay run information listed in Tables 3A, 3B, 3C, and 3D.

b) *A review of the data in Tables 3A, 3B, 3C, and 3D reveals that some runs, especially many repeat runs, appear to fail the quality control criteria per SOP 2D-11.2 without additional repeats run, as follows:*

(1) *For selegiline - Runs 47, Rep X, Rep AC;*
(2) *For desmethylselegiline - Runs Rep A, Rep B, Rep K, Rep L, Rep M, Rep Q, Rep V;*
(3) *For amphetamine - Runs 45/46, 15/24, Rep V, Rep Y;*
(4) *For methamphetamine - Runs 15/24, 26/33, Rep N, Rep Q, Rep AJ.*

Comment and explain why the samples were not repeated again.

c) *Tables 3A, 3B, 3C, and 3D state that the results for several re-assay analytical runs were not used in the final study data. Supply additional information identifying which samples were re-assayed on these runs, why the samples were re-assayed, and the reasons why the results of these re-assays were not used.*

Firm's Response #2a:

Tables of Repeat Sample Assays were revised as requested. Originally, ""*Because of the dissimilar range of concentrations of selegiline versus desmethylselegiline and methamphetamine to be determined, repeat analyses were required for samples in which desmethylselegiline and methamphetamine may have . . . These samples were routinely re-analyzed and were not reported in the repeat tables.*" *These samples which may have . . . account for roughly 95% of the additional samples that are shown in the expanded Tables 3A-D but not reported in Tables 2A-D of the report.*"

Assay results that required further repeat assays, except for those due to . . were highlighted in the corrections tables. The revised assay Results Tables also included

the concentrations for the corresponding intensity ratios, and organized by assay runs, repeat runs as well as by subject number.

Division's Comment #2a:

The firm's response is adequate.

Firm's Response #2b: Fasting Study #1627(#95-A035B)

The original report was reviewed extensively. *"Required repeats were overlooked due to the complicated repeat criteria and errors in data entry, typing, rounding off, and repeat results not included were discovered."* In addition, three reruns RepAR, RepAS and RepAT were performed on October 21 and 22, 1997 on frozen controls and samples that required further repeat assays. Changes in the final data as well as newly repeat results were amended to the appropriate Results Tables.

The firm also responded to the questions concerning specific assays raised in the deficiency comments, item by item.

Run 47- Selegiline(S): Required repeats were included in RepAT.
Run RepX - S: Same as above.
Run RepAC - S: Same as above.
Run RepA, RepB, RepK, RepL, RepM, and RepQ - Desmethylselegiline(D): The high control was not acceptable; samples analyzed were all 4 times diluted and accepted per SOP.
Run RepV - D: Required repeat, 10-I-0.25, was included in RepAR.
Run 45,46 - Amphetamine(A): The runs were only for S/D/M.
Run 15,24 - A: The run was rejected for subject 15-II, repeated in RepAJ which was also rejected. Required repeats were included in RepAR and RepAS.
Run RepV - A: Required repeats were included in RepAR.
Run RepY - A: Required repeat, 17-II-0.5, was included in RepAR.
Run 15/24 - Methamphetamine (M): Required repeats were included in RepK, RepX, RepAJ and RepAR.
Run 26,33 - M: QC failed and the data for Subject 26-II were not used from this run, but from RepG.

Run RepN - M: Required repeats were included in RepAS.
Run RepQ - M: High QC failed but all samples were run 4 times diluted and accepted per SOP.

Run RepAJ - M: High QC failed, required repeats were included in RepAR.

Firm's Response #2c:

"The majority of these runs appeared in Tables 3A-D by mistake, because reassay required for one chemical generated computer calculated results for the other chemicals which should not be in the table."

Table 3A - Selegiline (S):

Runs RepY, RepAE, RepAF, RepAG, RepAJ and Rep AM were not for S.

Table 3B - Desmethylselegiline (D):

Runs RepAC, AD, AJ, AO were not for D. No data were used from runs RepI, U or AL because, respectively, inappropriate volumes of injection was used, incorrect dilution factor was used, and samples were repeated by error.

Table 3C - Amphetamine (A):

Runs Rep W, AC, AE were not for A. Run RepX was used for 1 I-IEI-72, 96, and 144 and added back to the amended tables.

Division's Comment #2b and 2c:

The firm's responses above are adequate.

Deficiency Comment #2 (Part Two: On Food Effect Study):

"In the Food Effects Study #1666 (#95-A035C) -

a) A review of the data in Tables 3A, 3B, 3C and 3D reveals that the following repeat runs appear to fail your quality control criteria, without additional repeats run, as follows:

(1) For desmethylselegiline - Run Rpt F;
(2) For amphetamine - Run Rpt E;
(3) For methamphetamine - Run Rpt F.

Comment and explain why the samples were not repeated again.

b) Tables 3C and 3D state that the results for some re-assay analytical runs were not used in the final study data. Supply additional information identifying which samples were re-assayed on these runs, why the samples were re-assayed, and the reasons why the results of these re-assays were not used."

Firm's Response #2a (Part Two):

The original report was extensively reviewed for errors. All required repeats were included in run Rptj performed October 21, 1997.

Table 3B - Desmethylselegiline (D):

Run Rpt F: High QC failed but all samples were diluted 4 times, and diluted QC was acceptable. Therefore, run was acceptable per SOP.

Table 3C - Amphetamine (A):

Run Rpt E: Required repeats were included in Rptj.

Table 3D - Methamphetamine (M):

Run Rpt F: same as Table 3B above.

Firm's Response #2b (Part Two):

Tables 3C - **Amphetamine** and 3D - **Methamphetamine** had labelling error, Rpt D should be Rpt C, which was run for S and D only, not for A or M. Run Rpt H was not run for M.

Division's Comment #2a and 2b (Part Two):

The firm's responses are acceptable.

Deficiency Comment #3:

"Your response to deficiency #7 is incorrect. The Division finds that the following subjects met the criteria for elimination from the final data:

> *For Treatment A (Stason Test Product) - #10, #12, #15, #16, #18, #20, #22, #26, #34, #36, #37, #44, and #45;*
>
> *For Reference Treatment B (Eldepril Tablets) - #2, #7, #11, #12, #15, #17, #20, #22, #34, and #37.*

Please note that you should have eliminated Subject #10 from the Test Treatment data set and should not have eliminated Subject #36 from the Reference Product data set. Recalculate the selegiline results using the correct data sets; include the revised SAS data files on diskette with the re-submission."

Firm's Response #3:

The firm reanalyzed the corrected data from both Fasted and Fed Studies. Especially, for the Fasted Study referred to in the deficiency comment above, the statistical re-analysis was performed with removal of subjects that met the following conditions: either with fewer than 4 measurable plasma selegiline concentrations reported, or whose first measurable plasma selegiline concentration was the observed CMAX.

Division's Comment #3:

The firm's response to this deficiency comment is adequate. Results from the

statistical reanalyses are summarized below (following the Response and Comment #4):

Deficiency Comment #4:

"The in vitro data demonstrates that this product meets USP 23 dissolution requirements. However, the submission states that a [redacted] will be used in the dissolution testing of validation batches of the test product, because the USP dissolution assay procedure is not appropriate for this product. Therefore, additional dissolution testing is needed to generate dissolution profiles for the test versus the reference product lots by reporting the dissolution at 5, 10, and 20 minutes, using USP 23 test conditions modified to use the proposed procedure."

Firm's Response #4:

Although it was stated in a previous submission that the firm intended to use the assay method, instead of the USP's HPLC method, for the dissolution testing of validation batches of the test product, *"this intention was not carried out. Instead the validation batches were tested using the USP dissolution method. Appended is a copy of the referenced test method (STM.038)."*

Division's Comment #4:

Although the appended method (STM.038) indicates that the USP's HPLC method was used as the analytical method for the dissolution testing, the dissolution testing procedure itself in the Stason's Standard Testing Method 038 is not the USP specified procedure, and 900 ml of dissolution medium is used instead of 500 ml as per USP 23, Suppl. 4, pp. 3180-1. The firm should revise the STM.038 to comply with the USP specifications.

The dissolution data for the test and reference products as submitted in the May 12, 1997 amendment are acceptable (See attachments). However, in the future the firm should provide dissolution profiles, with the minimum timepoints of 5, 10 and 20 minutes, for the tested products.

II. Fasting Study #1627(#95-A035B) Results of Pharmacokinetic and

Statistical Analyses :

For the study design and protocol, see Review of Fasting and Non-Fasting In-Vivo Bioequivalence Studies, Larry Ouderkirk, Submission Date of May 31, 1996 and Review Date of February 28, 1997.

Forty-seven of 48 enrolled subjects completed the clinical portion of the study. Subject #3 withdrew from the study during Phase II after he ingested analgesic drugs as treatment for pain of injuries received in an auto accident.

A. Selegiline Results:

Statistical analysis was performed on the corrected selegiline plasma data with the removal of the data from the following subjects with fewer than 4 measurable selegiline concentrations reported, or whose first measurable selegiline concentration was the observed CMAX: For the test formulation, Subjects #10, 12, 15, 16, 18, 20, 25, 26, 34, 36, 44, 45, and 47; for the reference formulation, Subjects #2, 7, 11, 12, 15, 17, 20, 22, 34, 37, and 46.

There was no significant difference (alpha=0.05) between treatments for lnAUC(0-T), lnAUC(0-Infinity), lnCMAX, TMAX, T1/2 or KEL. The results are summarized in the tables below:

Note: There are great differences between geometric LS means and arithmetic means of AUCs and CMAX (the results have been verified by reviewer) due to high inter-subject variability. CV% ranges from 90 to 111 for the test product, and from 71 to 76 for the reference product. Log-transformation of data reduces the variation magnitude and produces geometric means that are much smaller than the corresponding arithmetic means.

Table I

Selegiline Comparative Pharmacokinetic Parameters

Dose = 2x5 mg; n= 44

Parameters	Stason's Mean (CV%)	Elderpryl[R] Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	0.665* n=34	0.749* n=36	[0.67;1.17]	0.89
AUC (0-Inf) ng.hr/ml	0.722* n=15	0.889* n=16	[0.57;1.16]	0.81
CMAX(ng/ml)	0.737*	0.912*	[0.66;1.00]	0.81
TMAX (hrs)	0.73(20)	0.68(24)		
KEL (1/hrs)	1.03(82)	0.78(87)		
T1/2 (hrs)	1.53(101)	2.34(111)		

*Geometric LS Means

Table II

Comparative Mean Plasma Levels of Selegiline

ng/ml(CV%)

Dose = 2x5 mg; n = 44

Hour	Stason's	Eldepryl[R]
0	0	0
0.25	0.03(154)	0.10(260)
0.50	0.65(157)	1.00(103)
0.75	0.99(89)	1.07(702)
1.00	0.74(91)	0.57(92)
1.50	0.30(114)	0.23(96)
2.00	0.14(112)	0.11(73)
2.50	0.09(124)	0.07(94)
3.00	0.07(149)	0.05(93)
4.00	0.04(166)	0.03(107)
5.00	0.02(166)	0.02(128)
6.00	0.02(216)	0.01(183)
8.00	0.01(228)	0.01(213)
10.00	0.00(293)	0.01(345)
12.00	0.00(406)	0.00(600)
18.00	0.00(410)	0
24.00	0.00(409)	0
48.00	0	0
72.00	0	0
96.00	0	0
144.00	0	0
192.00	0	0
AUC(0-T)ng.hr/ml	1.21(111)	1.32(71)
AUC(0-Inf)ng.hr/ml	1.23(104)	1.18(76)
CMAX	1.16(90)	1.41(76)

B. Amphetamine:

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-T), AUC (0-Infinity), lnCMAX, TMAX, T1/2 and KEL. The results are summarized in the tables below:

Table III
Amphetamine Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 47

Parameters	Stason's Mean (CV%)	Eldepryl[R] Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	77.69*	76.84*	[0.97;1.06]	1.01
AUC (0-Inf) ng.hr/ml	81.50*	80.88*	[0.96;1.06]	1.01
CMAX(ng/ml)	2.87*	2.86*	[0.96;1.05]	1.00
TMAX (hrs)	4.68(51)	4.83(64)		
KEL (1/hrs)	0.045(22)	0.044(22)		
T1/2 (hrs)	15.87(20)	16.49(24)		

*Geometric LS Means

Table IV
Comparative Mean Plasma Levels of Amphetamine
ng/ml(CV%)
Dose = 2x5 mg; n= 47

Hour	Stason's	Eldepryl[R]
0	0	0
0.25	0.01(391)	0.04(440)
0.50	0.24(113)	0.39(104)
0.75	0.93(72)	1.15(55)
1.00	1.56(52)	1.53(37)
1.50	2.14(34)	2.08(27)
2.00	2.32(29)	2.25(23)
2.50	2.47(27)	2.37(23)
3.00	2.48(22)	2.42(28)
4.00	2.48(21)	2.45(23)
5.00	2.49(23)	2.45(21)
6.00	2.50(27)	2.38(24)
8.00	2.44(22)	2.38(18)
10.00	2.36(22)	2.29(19)
12.00	2.16(24)	2.19(30)
18.00	1.88(28)	1.82(25)
24.00	1.33(33)	1.37(26)
48.00	0.44(42)	0.49(42)
72.00	0.17(94)	0.17(67)
96.00	0.04(170)	0.03(215)
144.00	0(686)	0.01(480)
192.00	0.01(443)	0
AUC(0-T)ng.hr/ml	80.03(26)	78.83(24)
AUC(0-Inf)ng.hr/ml	82.77(24)	81.84(21)
CMAX	2.94(21)	2.93(23)

C. Methamphetamine:

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-T), lnAUC (0-Infinity), lnCMAX, TMAX, T1/2 and KEL. The results are summarized in the tables below:

Table V
Methamphetamine Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 47

Parameters	Stason's Mean (CV%)	Eldepryl[R] Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	181.0*	183.6*	[0.95;1.02]	0.98
AUC (0-Inf) ng.hr/ml	185.5*	187.7*	[0.95;1.02]	0.99
CMAX(ng/ml)	8.926*	8.697*	[0.99;1.06]	1.03
TMAX (hrs)	3.48(64)	3.17(48)		
KEL (1/hrs)	0.052(23)	0.051(22)		
T1/2 (hrs)	13.94(21)	14.34(24)		

*Geometric LS Means

Table VI

Comparative Mean Plasma Levels of Methamphetamine ng/ml(CV%)

Dose = 2x5 mg; n= 47

Hour	Stason's	Eldepryl[R]
0	0	0
0.25	0.01(501)	0.09(416)
0.50	0.96(104)	1.59(103)
0.75	3.46(61)	4.45(50)
1.00	5.32(42)	5.70(33)
1.50	7.40(27)	7.15(22)
2.00	7.90(22)	7.57(22)
2.50	7.97(23)	7.93(19)
3.00	7.94(20)	7.80(21)
4.00	7.70(24)	7.52(19)
5.00	7.46(23)	7.26(22)
6.00	6.93(23)	6.79(24)
8.00	6.34(23)	6.47(22)
10.00	6.13(23)	6.09(20)
12.00	5.53(26)	5.53(25)
18.00	4.19(34)	4.18(25)
24.00	2.89(36)	2.97(32)
48.00	0.78(54)	0.84(56)
72.00	0.27(77)	0.29(85)
96.00	0.07(138)	0.08(137)
144.00	0.02(525)	0.01(486)
192.00	0.02(517)	0
AUC(0-T)ng.hr/ml	188.2(29)	189.8(28)
AUC(0-Inf)ng.hr/ml	189.6(29)	197.5(27)
CMAX	9.11(20)	8.82(17)

D. Desmethylselegiline:

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-T), lnAUC (0-Infinity), lnCMAX, T1/2 or KEL. There was significant difference between treatments for TMAX (p=0.0102). The results are summarized in the tables below:

Table VII
Desmethylselegiline Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 47

Parameters	Stason's Mean (CV%)	Eldepryl[R] Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	38.87*	39.43*	[0.95;1.02]	0.99
AUC (0-Inf) ng.hr/ml	42.20*	43.03*	[0.94;1.03]	0.98
CMAX(ng/ml)	14.83*	14.99*	[0.94;1.04]	0.99
TMAX (hrs)	0.93(30)	0.81(23)		
KEL (1/hrs)	0.087(36)	0.084(34)		
T1/2 (hrs)	8.83(32)	9.55(46)		

*Geometric LS Means

Table VIII
Comparative Mean Plasma Levels of Desmethylselegiline
ng/ml(CV%)
Dose = 2x5 mg; n= 47

Hour	Stason's	Eldepryl[R]
0	0	0
0.25	0.42(230)	1.13(226)
0.50	7.27(827)	9.15(61)
0.75	13.61(39)	14.61(30)
1.00	9.85(32)	13.13(30)
1.50	6.92(32)	9.18(36)
2.00	5.37(35)	6.69(37)
2.50	4.17(40)	5.10(35)
3.00	2.84(44)	4.15(39)
4.00	1.91(43)	2.73(36)
5.00	1.56(44)	1.82(36)
6.00	1.00(40)	1.55(40)
8.00	0.72(46)	1.05(41)
10.00	0.61(55)	0.72(42)
12.00	0.38(58)	0.61(52)
18.00	0.22(61)	0.38(48)
24.00	0.01(300)	0.22(61)
48.00	0	0.03(258)
72.00	0	0
96.00	0	0
144.00	0	0
192.00	0	0
AUC(0-T)ng.hr/ml	41.24(34)	41.42(31)
AUC(0-Inf)ng.hr/ml	44.87(31)	46.01(29)
CMAX	15.62(32)	15.65(28)

Adverse Effects: See L. Ouderkirk's review of the initial submission dated May 31,

1996.

III. Non-Fasting Study #1666(#95-A035C) Results of Pharmacokinetic and Statistical Analyses :

For the study design and protocol, see Review of Fasting and Non-Fasting In-Vivo Bioequivalence Studies, Larry Ouderkirk, Submission Date of May 31, 1996 and Review Date of February 28, 1997.

Twenty-three of 24 enrolled subjects completed the clinical portion of the study. Subject #19 did not return for Phase II of the study for unknown reasons.

Data from all analytes, selegiline, desmethylselegiline, amphetamine and methamphetamine required correction. However, since correction for desmethylselegiline was insignificant and data reanalysis yielded the same results, the results will not be summarized below. For the results of desmethylselegiline of the food study, see L. Ouderkirk's review of submission dated May 31, 1996 (A summary is attached to the current review.).

Selegiline Results (With Corrected Data):

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-Infinity), lnCMAX, TMAX, T1/2 and KEL. There were significant difference between treatments for lnAUC(0-T) (p=0.0001). The results are summarized in the tables below:

NOTE: In this current amendment, the firm recalculated KEL, T1/2 and AUC(0-Infinity) with no explanation for the different criteria used compared with that stated in the last amendment (dated May12, 1997). However, the results of the statistical analysis of the recalculated (log-transformed) AUC(0-Infinity) data are similar to that reported in the previous amendment, and there were not sufficient subjects included in the statistical analysis for the lnAUC(0-Infinity) of selegiline to be considered a reliable parameter for bioequivalence consideration.

Table IX
Selegiline Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 23
Non-Fasting Study

Parameters	Stason's(fed) Mean (CV%)	Eldepryl^{R}(fed) Mean (CV%)	Stason's(fasted) Mean (CV%)	Ratio T/R (fed/fed)
AUC (0-T) ng.hr/ml	2.00*	2.38*	1.12*	0.84
AUC (0-Inf) ng.hr/ml	2.22* n=6	2.48* n=8	1.48* n=5	0.89
CMAX(ng/ml)	0.913*	0.910*	0.750*	1.00
TMAX (hrs)	1.17(48)	1.14(56)	0.89(46)	
KEL (1/hrs)	0.353(71) n=6	0.466(95) n=8	0.848(93) n=5	
T1/2 (hrs)	6.59(166) n=6	4.50(110) n=8	9.96(186) n=5	

*Geometric LS Means

Table X

Comparative Mean Plasma Levels of Selegiline

ng/ml(CV%)

Dose = 2x5 mg; n= 23

Non-Fasting Study

Hour	Stason's(fed)	Eldepryl[R](fed)	Stason's(fasted)
0	0	0	0
0.25	0.15(234)	0.25(333)	0.04(201)
0.50	1.34(204)	0.90(159)	0.63(193)
0.75	1.94(196)	1.12(129)	1.33(150)
1.00	1.35(165)	1.09(133)	0.96(125)
1.50	0.98(153)	0.98(138)	0.60(140)
2.00	0.79(163)	1.00(172)	0.41(168)
2.50	0.61(133)	0.64(173)	0.33(175)
3.00	0.43(146)	0.54(156)	0.29(196)
4.00	0.31(154)	0.38(178)	0.20(208)
5.00	0.24(159)	0.26(186)	0.14(200)
6.00	0.17(166)	0.15(188)	0.09(203)
8.00	0.12(136)	0.11(186)	0.07(223)
10.00	0.07(142)	0.07(184)	0.04(187)
12.00	0.05(149)	0.05(170)	0.03(166)
18.00	0.03(184)	0.02(221)	0.02(170)
24.00	0.02(177)	0.02(232)	0.01(176)
48.00	0.02(194)	0.01(203)	0.01(230)
72.00	0.00(354)	0.01(271)	0.01(226)
96.00	0.00(355)	0.01(276)	0.00(480)
AUC(0-T)ng.hr/ml	5.47(151)	5.30(143)	3.41(157)
AUC(0-Inf)ng.hr/ml	6.71(211)	6.54(155)	2.62(183)
CMAX	2.28(162)	1.56(114)	1.46(134)

Methamphetamine Results (With Corrected Data):

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-T), lnAUC (0-Infinity), lnCMAX, TMAX, T1/2 and KEL. The results are summarized in the tables below:

Table XI
Methamphetamine Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 23
Non-Fasting Study

Parameters	Stason's(fed) Mean (CV%)	Eldepryl[R](fed) Mean (CV%)	Stason's(fasted) Mean (CV%)	Ratio T/R (fed/fed)
AUC (0-T) ng.hr/ml	166.4*	174.9*	170.6*	0.95
AUC (0-Inf) ng.hr/ml	171.8*	180.2*	174.8*	0.95
CMAX(ng/ml)	8.48*	8.82*	9.15*	0.96
TMAX (hrs)	3.73(34)	3.87(40)	3.59(50)	
KEL (1/hrs)	0.051(26)	0.050(25)	0.050(26)	
T1/2 (hrs)	14.34(24)	14.64(27)	14.83(26)	

*Geometric LS Means

Table XII

Comparative Mean Plasma Levels of Methamphetamine

ng/ml(CV%)

Dose = 2x5 mg; n= 23

Non-Fasting Study

Hour	Stason's(fed)	Eldepryl[R](fed)	Stason's(fasted)
0	0	0	0
0.25	0.02(351)	0.10(311)	0.02(351)
0.50	0.74(143)	1.22(121)	0.54(154)
0.75	2.09(109)	2.76(76)	2.47(84)
1.00	3.10(71)	3.69(65)	4.49(48)
1.50	5.05(38)	5.20(41)	6.57(30)
2.00	6.08(27)	6.29(33)	7.45(24)
2.50	7.07(18)	7.06(24)	8.22(30)
3.00	7.62(19)	7.75(16)	7.70(20)
4.00	8.08(19)	8.29(16)	7.99(20)
5.00	7.98(17)	8.51(15)	7.42(20)
6.00	7.61(19)	7.37(16)	7.08(19)
8.00	6.98(20)	7.10(17)	7.11(28)
10.00	5.33(29)	5.70(25)	5.35(24)
12.00	4.01(33)	4.22(26)	3.94(25)
18.00	2.78(38)	2.72(26)	2.77(25)
24.00	1.31(43)	1.40(39)	1.35(32)
48.00	0.67(53)	0.66(43)	0.68(45)
72.00	0.21(70)	0.21(58)	0.22(64)
96.00	0.06(167)	0.05(166)	0.08(120)
AUC(0-T)ng.hr/ml	172.2(27)	177.8(18)	175.2(24)
AUC(0-Inf)ng.hr/ml	178.5(27)	182.1(18)	180.0(24)
CMAX	8.59(15)	8.89(13)	9.40(26)

Amphetamine Results (With Corrected Data):

There was no significant difference (alpha=0.05) between treatments for lnAUC (0-T), lnAUC (0-Infinity), lnCMAX, TMAX, T1/2 and KEL. The results are summarized in the tables below:

Table XIII
Amphetamine Comparative Pharmacokinetic Parameters
Dose = 2x5 mg; n = 23
Non-Fasting Study

Parameters	Stason's(fed) Mean (CV%)	Eldepryl[R](fed) Mean (CV%)	Stason's(fasted) Mean (CV%)	Ratio T/R (fed/fed)
AUC (0-T) ng.hr/ml	71.83*	74.99*	73.70*	0.96
AUC (0-Inf) ng.hr/ml	77.09*	78.86*	78.27*	0.98
CMAX(ng/ml)	3.01*	3.09*	3.24*	0.97
TMAX (hrs)	5.41(29)	5.00(33)	5.24(48)	
KEL (1/hrs)	0.046(33)	0.051(34)	0.045(21)	
T1/2 (hrs)	16.93(42)	15.15(33)	15.97(20)	

*Geometric LS Means

Table XIV
Comparative Mean Plasma Levels of Amphetamine
ng/ml(CV%)
Dose = 2x5 mg; n= 23
Non-Fasting Study

Hour	Stason's(fed)	Eldepryl^{R}(fed)	Stason's(fasted)
0	0	0	0
0.25	0.02(480)	0.03(264)	0
0.50	0.18(156)	0.31(143)	0.11(203)
0.75	0.53(103)	0.71(84)	0.76(111)
1.00	0.88(68)	0.97(67)	1.29(58)
1.50	1.44(41)	1.51(46)	1.95(36)
2.00	1.83(33)	1.90(38)	2.25(29)
2.50	2.23(22)	2.21(28)	2.68(36)
3.00	2.45(25)	2.48(21)	2.50(23)
4.00	2.71(24)	2.74(22)	2.89(36)
5.00	2.85(26)	2.98(20)	2.62(23)
6.00	2.74(22)	2.68(27)	2.57(23)
8.00	2.62(24)	2.72(25)	2.69(32)
10.00	2.18(32)	2.35(25)	2.24(28)
12.00	1.81(31)	1.96(25)	1.80(24)
18.00	1.37(33)	1.38(27)	1.35(25)
24.00	0.73(36)	0.75(23)	0.76(30)
48.00	0.41(44)	0.39(38)	0.43(37)
72.00	0.16(86)	0.13(83)	0.13(73)
96.00	0.03(234)	0.02(280)	0.02(267)
AUC(0-T)ng.hr/ml	74.54(29)	76.26(20)	75.53(24)
AUC(0-Inf)ng.hr/ml	78.01(23)	81.25(20)	80.66(24)
CMAX	3.07(21)	3.13(21)	3.37(33)

Adverse Effects: See L. Ouderkirk's review of the initial submission dated May 31, 1996.

IV. Comments:

1. The firm's responses to the Division's Deficiency Comments are considered adequate and acceptable.

2. The single-dose, fasting bioequivalence study and the single-dose, non-fasting bioequivalence study conducted by Stason on the test product, Selegiline HCl Tablets, USP, 5 mg, lot # PK5001, comparing it with the reference product, Eldepryl[R] Tablets, USP, 5 mg, lot # 3B002J, demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) of **amphetamine, methamphetamine** and **desmethylselegiline, under both fasting and non-fasting conditions.**

The study results of selegiline were reported but the pivotal statistical criteria were not applied to the parent drug data, as stated in the Bioequivalence Guidance of Selegiline HCl Tablets (issued December 22, 1995). The mean ratios of the test to reference product for AUC(0-T), AUC(0-Infinity) and CMAX were within [.80-1.20] limit for both fasting and non-fasting studies.

3. The in vitro dissolution data for the test product are acceptable. However, the firm should revise the Standard Testing Method #038 to comply with the USP specifications concerning **the USP's HPLC analytical assay method** and the dissolution procedure, specifically, the volume of the dissolution medium of **500 ml** instead of 900 ml. In the future, the firm should also submit the dissolution data as dissolution **profile of a minimum of 3 time points (e.g., 5, 10 and 20 minutes)** instead of only a single-point dissolution data.

V. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose, non-fasting bioequivalence study conducted by Stason Pharmaceuticals on the test product, Selegiline HCl Tablets, USP, 5 mg, lot # PK5001, comparing it with the reference product, Eldepryl[R] Tablets, USP, 5 mg, lot # 3B002J, have been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting and non-fasting conditions. The

test product, Stason's Selegiline H Cl Tablets USP, 5 mg, is deemed bioequivalent to the reference product, Eldepryl® Tablets, 5 mg, manufactured by Somerset Pharmaceuticals.

2. The in-vitro dissolution testing conducted by Stason Pharmaceuticals on its Selegiline HCl Tablets, USP, 5 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of water at 37°C using USP XXIII apparatus I(basket) at 50 rpm. The test product should meet the following specifications:

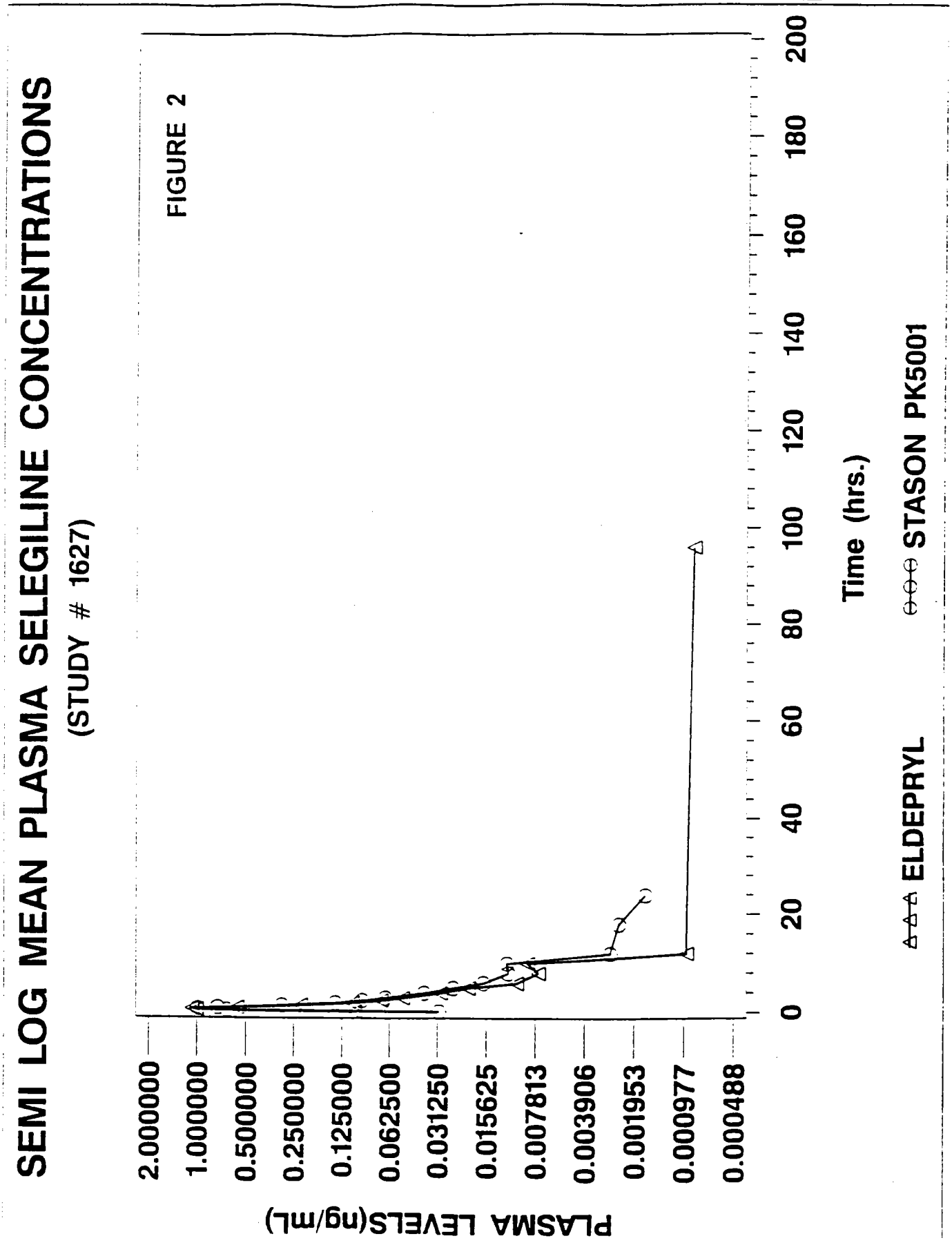
Not less than of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/25/98

Concur: Date: 1/26/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

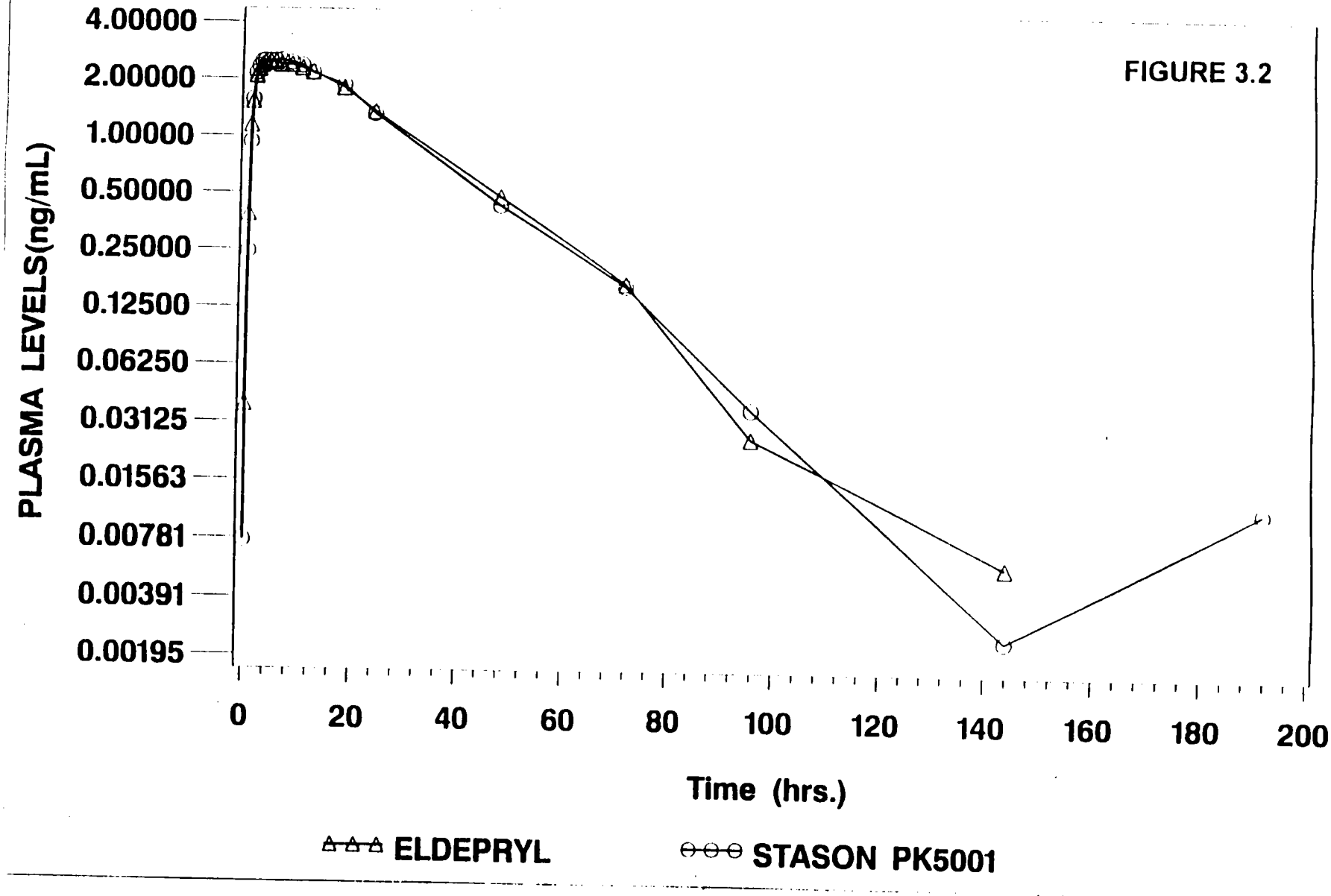
Attachments: 12 pages
cc: ANDA # 74-912 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
Hnguyen/01-23-98/WP#74912sd.d97 and
X:\new\firmsnz\stason\ltrs&rev\74912sd.d97


SEMI LOG MEAN PLASMA SELEGILINE CONCENTRATIONS
(STUDY # 1627)
FIGURE 2
PLASMA LEVELS(ng/mL)
2.000000
1.000000
0.500000
0.250000
0.125000
0.062500
0.031250
0.015625
0.007813
0.003906
0.001953
0.000977
0.000488
0
20
40
60
80
100
120
140
160
180
200
Time (hrs.)
ELDEPRYL
STASON PK5001

SEMI LOG MEAN PLASMA AMPHETAMINE CONCENTRATIONS

(STUDY # 1627)

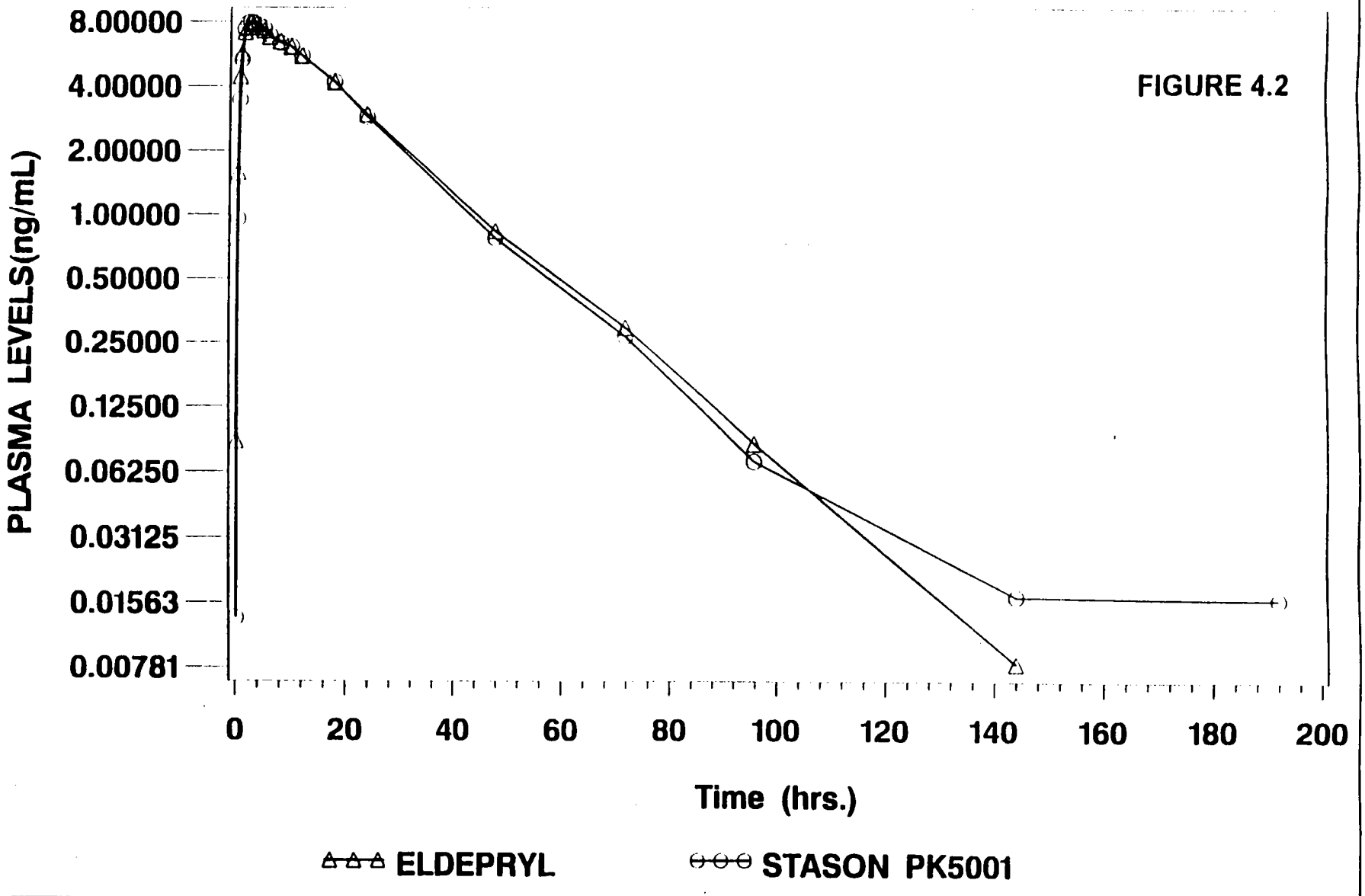
FIGURE 3.2



SEMI LOG MEAN PLASMA METHAMPHETAMINE CONCENTRATIONS

(STUDY # 1627)

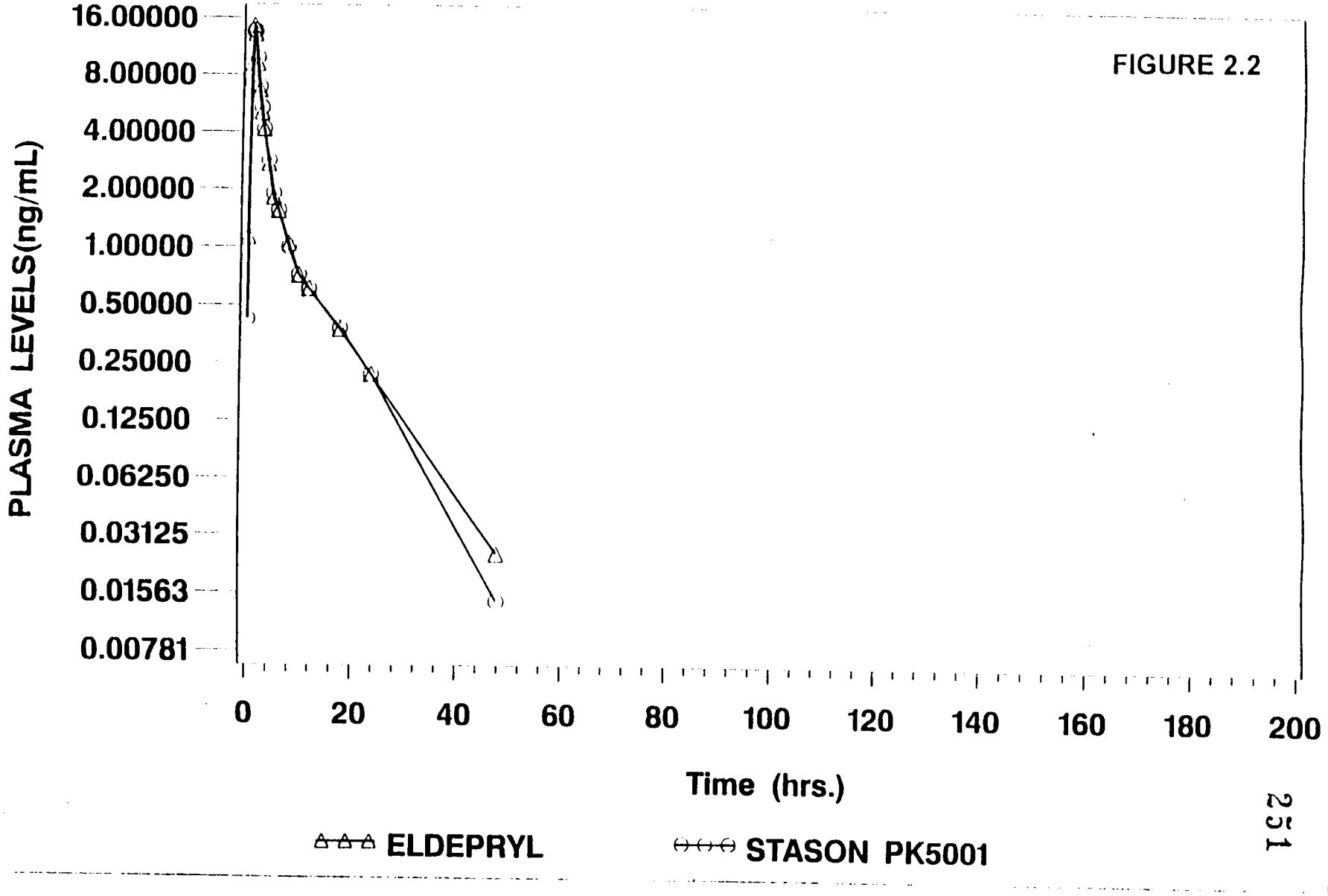
FIGURE 4.2

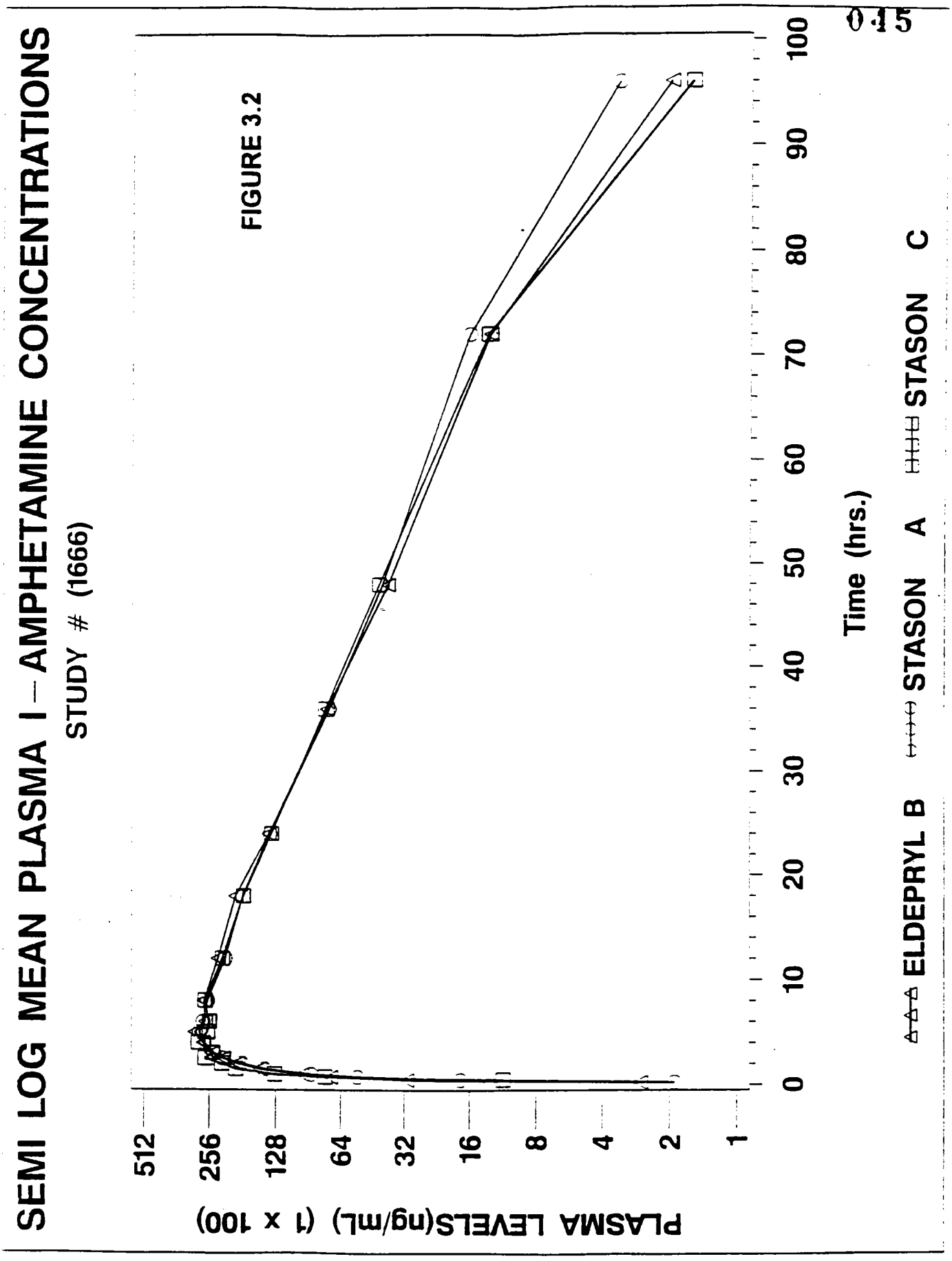


SEMI LOG MEAN PLASMA N-DESMETHYLSELEGILINE CONCENTRATIONS

(STUDY # 1627)

FIGURE 2.2




SEMI LOG MEAN PLASMA I – AMPHETAMINE CONCENTRATIONS
STUDY # (1666)
FIGURE 3.2
PLASMA LEVELS(ng/mL) (1 x 100)
512
256
128
64
32
16
8
4
2
1
0
10
20
30
40
50
60
70
80
90
100
Time (hrs.)
ELDEPRYL B
STASON A
STASON C

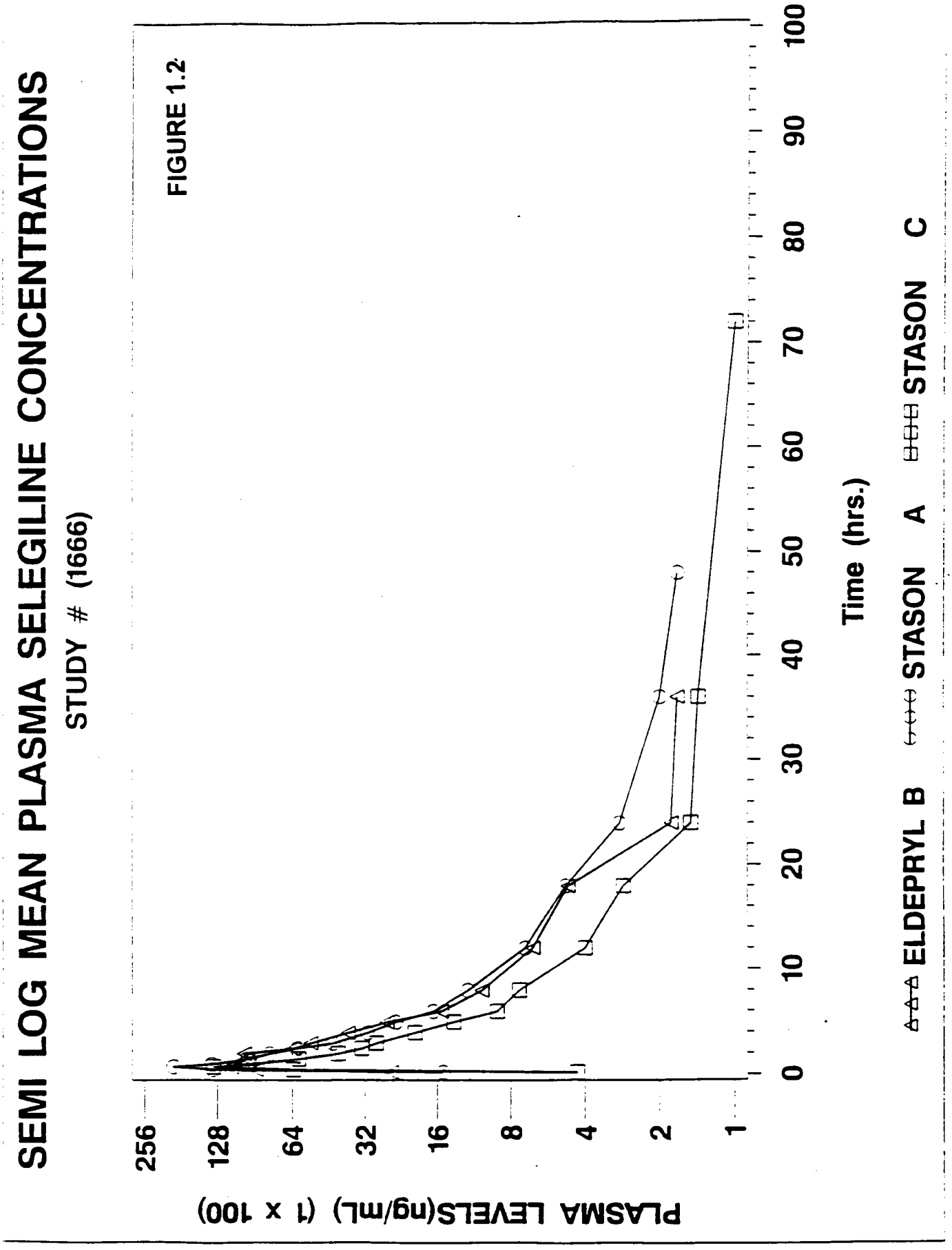

SEMI LOG MEAN PLASMA SELEGILINE CONCENTRATIONS
STUDY # (1666)
FIGURE 1.2
PLASMA LEVELS(ng/mL) (1 x 100)
256
128
64
32
16
8
4
2
1
0
10
20
30
40
50
60
70
80
90
100
Time (hrs.)
ELDEPRYL B
STASON A
STASON C

TABLE 19

IN VIVO FOOD EFFECT STUDY NO. 1566 - 23 SUBJECTS

DESMETHYLSELEGILINE - ARITHMETIC MEAN PLASMA LEVELS [NG/ML] VERSUS TIME (CV%)

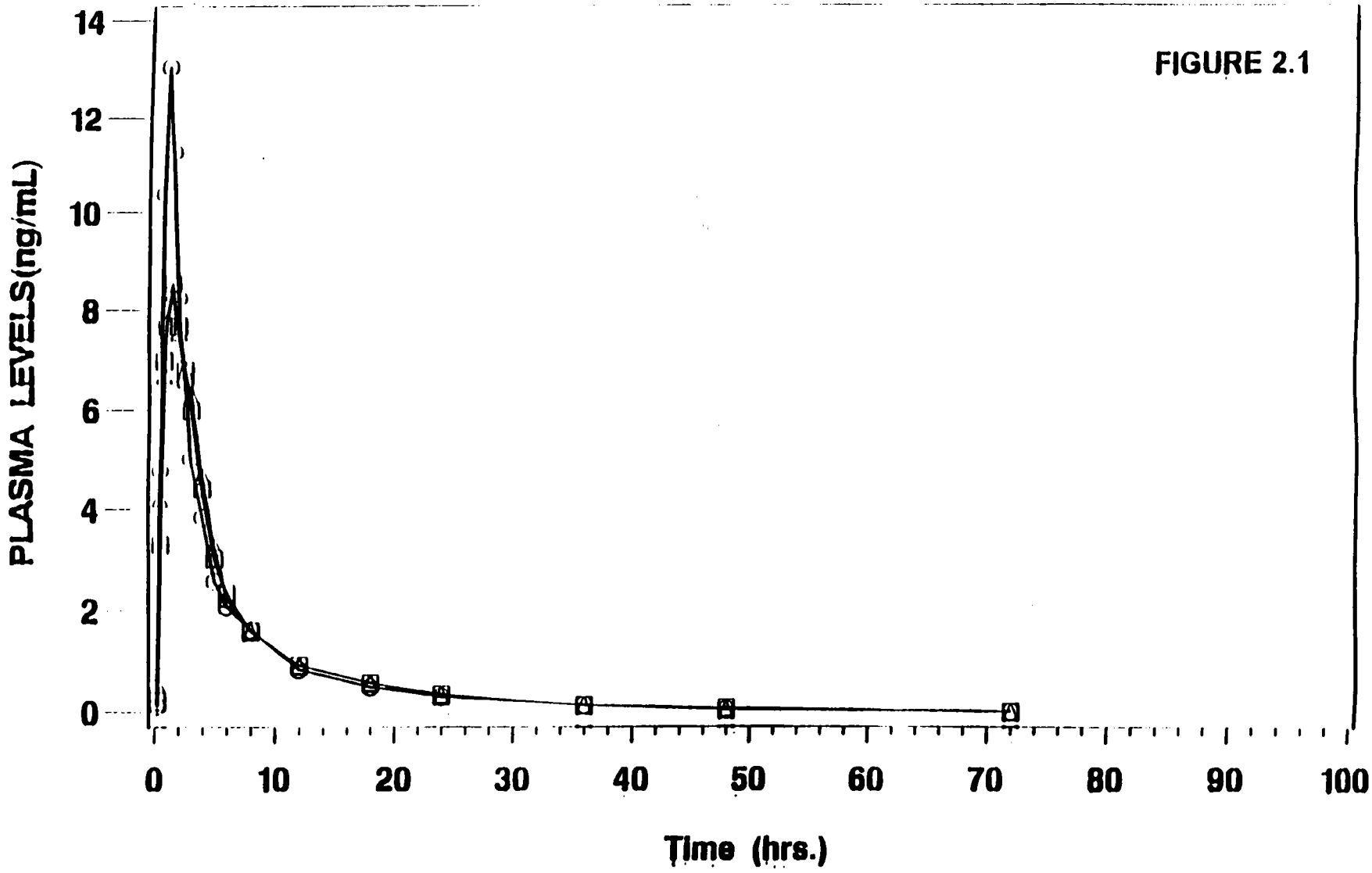
TIME (HR)	FED TEST (TREATMENT A)	FED REFERENCE (TREATMENT B)	FASTED TEST (TREATMENT C)	RATIO (A/B)	RATIO (A/C)
0	0.00	0.00	0.00	----	----
0.25	0.21 (319)	0.56 (209)	0.12 (325)	0.38	1.75
0.5	3.30 (147)	4.22 (85)	4.79 (104)	0.78	0.69
0.75	6.98 (99)	6.70 (61)	10.38 (48)	1.04	0.67
1.0	7.68 (62)	7.76 (53)	13.05 (35)	0.99	0.59
1.5	8.56 (39)	8.36 (43)	11.27 (37)	1.02	0.76
2.0	7.68 (40)	7.56 (37)	8.25 (42)	1.02	0.93
2.5	6.80 (43)	6.80 (40)	6.57 (45)	1.00	1.04
3.0	6.00 (42)	6.27 (45)	5.04 (52)	0.96	1.19
4.0	4.42 (50)	4.68 (51)	3.84 (58)	0.94	1.15
5.0	3.02 (56)	3.27 (53)	2.57 (71)	0.92	1.18
6.0	2.34 (66)	2.25 (56)	2.08 (77)	1.04	1.13
8.0	1.61 (71)	1.60 (64)	1.63 (102)	1.01	0.99
10.0	0.92 (77)	0.92 (70)	0.84 (77)	1.00	1.10
12.0	0.57 (76)	0.57 (68)	0.49 (72)	1.00	1.16
18.0	0.35 (78)	0.33 (73)	0.30 (82)	1.06	1.17
24.0	0.13 (132)	0.13 (117)	0.13 (118)	1.00	1.00
48.0	0.08 (179)	0.05 (192)	0.04 (213)	1.60	2.00
72.0	0.01 (340)	0.00	0.00	----	----
96.0	0.00	0.00	0.00	----	----

Figure - 6

MEAN PLASMA N-DESMETHYLSELEGILINE CONCENTRATIONS

STUDY # (1666)

FIGURE 2.1



Attachment 8

TABLE 21

IN VIVO FOOD EFFECT STUDY NO. 1566 - 23 SUBJECTS

DESMETHYLSELEGILINE - LEAST-SQUARES MEANS FOR PK PARAMETERS (CV%)

PARAMETER	FED TEST (TREATMENT A)	FED REFERENCE (TREATMENT B)	FASTED TEST (TREATMENT C)	RATIO (A/B)	RATIO (A/C)
ln AUC(T) [ng•hr/mL]	3.76	3.80	3.79	----	----
(Geomet. mean)	42.91	44.79	44.30	0.96	0.97
ln AUC(I) [ng•hr/mL]	3.83	3.86	3.85	----	----
(Geomet. mean)	45.92	47.58	47.00	0.97	0.98
ln Cmax [ng/mL]	2.28	2.28	2.63	----	----
(Geomet. mean)	9.73	9.76	13.87	1.00	0.70
Tmax [hr]	1.54	1.72	1.13	0.90	1.36
Kel [1/hr]	0.067	0.076	0.070	0.88	0.95
$T_{1/2}$ [hr]	12.16	10.45	10.70	1.16	1.14

SEMI LOG MEAN PLASMA l-METHAMPHETAMINE CONCENTRATIONS

STUDY # (1666)

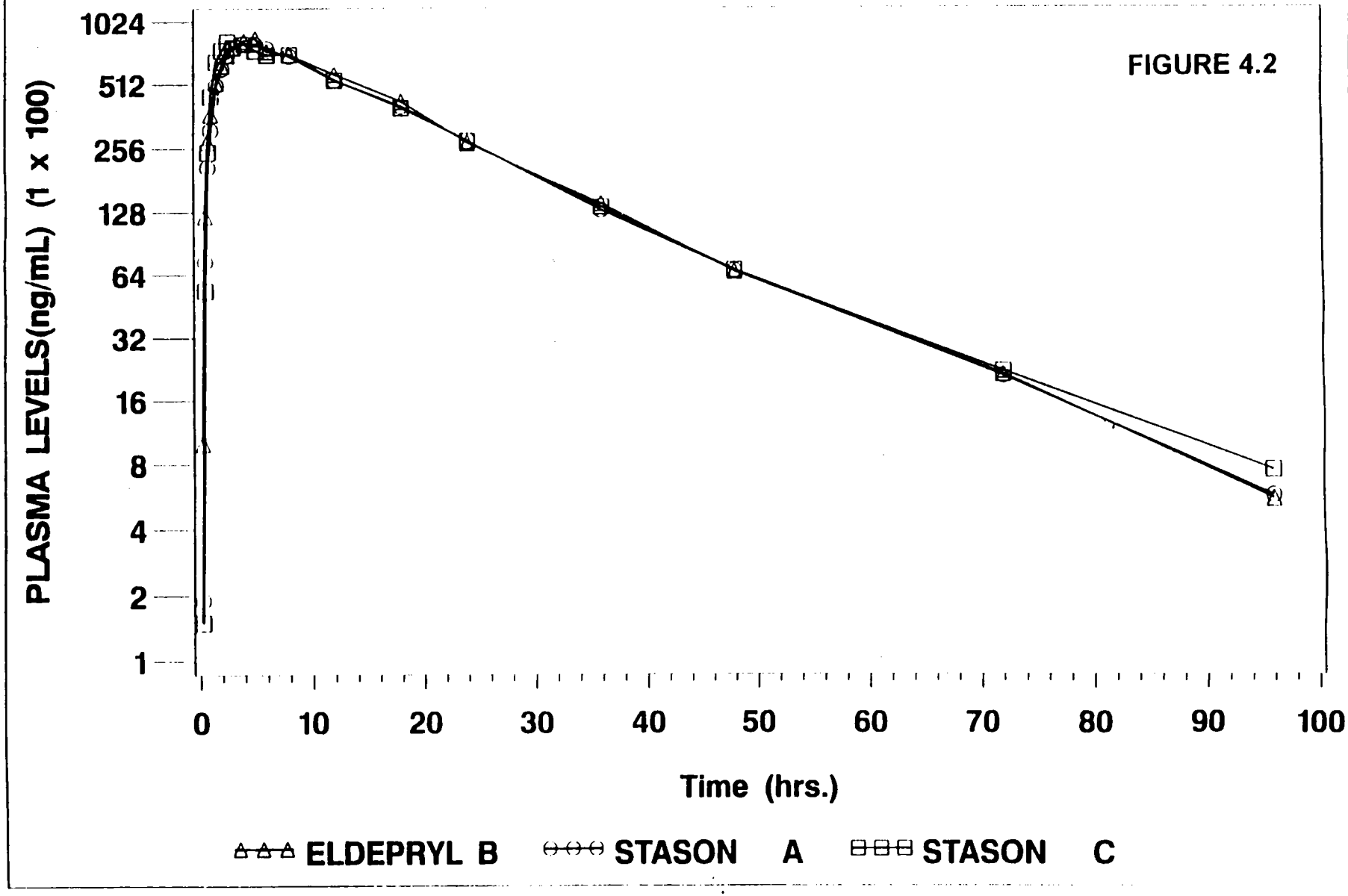


TABLE 28

PRODUCT FORMULATION - SELEGILINE TABLETS, 5 MG

(STASON INDUSTRIAL CORPORATION)

INGREDIENT	STANDARD	AMOUNT (MG/TAB)	PERCENT OF TABLET WEIGHT
SELEGILINE HCL	USP	5.00	3.85
MICROCRYSTALLINE CELLULOSE	NF		
LACTOSE MONOHYDRATE	NF		
STEARIC ACID	NF		
TABLET WEIGHT		130.00 MG	100.0%

Proposed Batch Size =

Table 4 - In Vitro Dissolution Testing

Drug (Generic Name):	Selegiline HCL Tablets
Dose Strength:	5 mg
ANDA No.:	74-912
Firm:	Stason Industrial Corp.
Submission Date:	5/12/97
File Name:	WP #74912o.597

I. Conditions for Dissolution Testing: (USP 23, Suppl. 4 pp. 3180-1)

Apparatus:	I (Basket)
RPM:	50
No. Units Tested:	12
Medium:	Water
Volume:	500 mL
Reference Drug:	Eldepryl® Tablets, 5 mg
Tolerance:	NLT Q) in 20 minutes
Assay Procedure:	HPLC (USP Procedure); Firm's Procedure)

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PK5001H Strength: 5 mg			Reference Product Lot # 3B002J Strength: 5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
20 (Sa)	USP - 84.7 Stason - 96.7		5.4 4.0	USP - 87.9 Stason - 111		5.4 5.0

BIOEQUIVALENCY ACCEPTABLE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74-912 APPLICANT:Stason Pharmaceuticals

DRUG PRODUCT: Selegiline HCl Tablet USP, 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

> In the future, you should also submit the dissolution data as dissolution **profile of a minimum of 3 time points (e.g., 5, 10 and 20 minutes)** instead of only a single-point dissolution data.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 74-912
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ Hnguyen

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Printed in final on / /98

Endorsements: (Final with Dates)
HFD-652/ Hnguyen
HFD-652/ YHuang 1/26/98
HFD-650/ D. Conner 1/26/98

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 5mg
Clinical
Analytical
Outcome: AC

2. **FOOD STUDY** (STP) Strengths: 5mg

Clinical:
Analytical:
Outcome: AC

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete
WINBIO COMMENTS: